

EDUCATIONAL OBJECTIVES

At the end of this continuing education activity, pharmacists will be able to

- Describe appropriate vancomycin usage in pediatric patients
- Discuss the 2020 guideline for vancomycin treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections for pediatric patients
- Describe vancomycin-induced acute kidney injury and how it affects vancomycin dosing and monitoring recommendations for pediatric patients

At the end of this continuing education activity, pharmacy technicians will be able to

- Describe conditions under which vancomycin is used in pediatric patients
- Define terms associated with vancomycin treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections for pediatric patients
- List important facts about vancomycin including trough level ranges and maximum doses
- Recognize how pharmacists dose and monitor vancomycin



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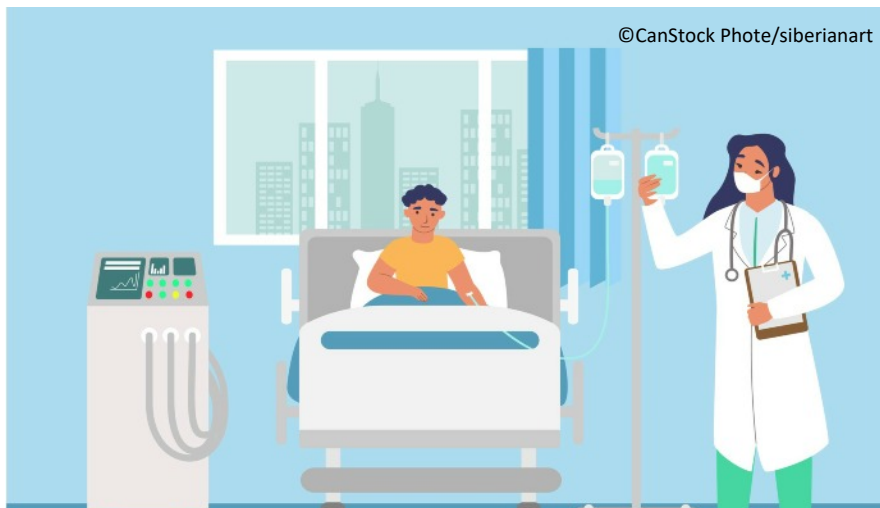
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Patient Safety: Safety of Vancomycin Dosing and AUC-Guided Dose Adjustments in Pediatric Patients

ABSTRACT: In 2020, new vancomycin guideline recommended monitoring for children primarily based on data suggesting an association between increasing AUC₂₄ with kidney injury. Researchers have reported several risk factors that increase a pediatric patient's chance of developing nephrotoxicity, including higher cumulative vancomycin dose. Past data suggested that overall vancomycin exposures (determined by trough monitoring) may have been higher than needed for adults, but common pediatric empiric dosing may have been too low. While the guideline provides vancomycin dosing for pediatric patients, it only covers disease caused by severe MRSA infections.

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INTRODUCTION

Vancomycin is a glycopeptide antibiotic used to treat infections caused by resistant gram-positive bacteria. Its mechanism of action is to attack bacterial cell walls. Clinically, healthcare providers have a healthy respect for vancomycin because it is an essential antimicrobial, but it can be quite toxic; it's critical to limit its use to appropriate situations. Clinicians must incorporate dosing and monitoring considerations from recent literature and guidelines to limit its toxicity. Vancomycin is indicated for a variety of infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), infective endocarditis as the alternative agent for penicillin-resistant *Streptococcus* species, and bacterial meningitis caused by *Streptococcus pneumoniae* and resistant *Enterococcus* species.^{1,2} The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists updated their 2009 guideline on June 1, 2020. In this iteration, they included the Pediatric

PAUSE AND PONDER: How does your hospital define acute kidney injury for pediatric patients?

ric Infectious Diseases Society. It addresses vancomycin use in serious infections, such as pneumonia, pyomyositis, multifocal osteomyelitis, complicated bacteremia, and necrotizing fasciitis and complicated infections when clinicians suspect MRSA.³

Table 1 summarizes vancomycin dosing for these infections. The new guideline incorporates pediatric patients, while the old guideline included only adults.^{3,4} The **Tech Talk Sidebar** (page 3) explains terms used throughout this activity.

2020 Guideline Overview

The 2020 guideline provides specific recommendations regarding vancomycin use and monitoring for serious MRSA infections. During 2009 guideline development, insufficient data was available to support any pediatric recommendation and all published data were from adults. Regardless, prescribers routinely used doses of 45 to 60 mg/kg/day divided every six to eight hours for pediatric patients, with some institutions implementing maximum doses and others not.³ At that time, most clinicians monitored trough concentrations in pediatric and adult patients, targeting 10 to 20 mg/L. The 2009 guideline suggested concentrations of 15 to 20 mg/L (but not less than 10 mg/L) as a surrogate marker for AUC₂₄/MIC drug exposure of 400 in adult patients.⁴ Due to lengthy calculations required to estimate vancomycin AUC₂₄ exposure, the 2009 guideline suggested trough monitoring only. It established a trough goal of not less than 10 mg/L to prevent poor clinical outcome and avoid increased bacterial resistance.^{4,5}

Table 2 (page 4) lists resources addressing a variety of different pediatric patients and correlates dosing regimens to their

troughs and/or AUC values. Clinicians can use this information if they do not have Bayesian calculators. In the 2009 guideline, the AUC₂₄/MIC goal of greater than 400 assumed infections responsive to a MIC of 1 mg/L. In adult patients, maintaining an appropriate AUC₂₄ is associated with improved efficacy and reduced nephrotoxicity.³

VANCOMYCIN-INDUCED ACUTE KIDNEY INJURY IN PEDIATRIC POPULATIONS

Nephrotoxicity is one of vancomycin's most common and worrisome adverse effects. In children, 5% to 43% experience nephrotoxicity.³ Vancomycin's most probable mechanism of kidney damage is direct insult to the renal tubules through oxidative stress due to increased reactive oxygen species (ROS).¹³ ROS play a role in cell signaling, but when their production increases or removal from the body is impaired, ROS can damage cells and tissues. When vancomycin accumulates in the kidneys, kidney cells die because ROS increase to untenable levels. It is important to reduce the likelihood of excess ROS, especially in children, as nephrotoxicity can have lifelong consequences.¹⁴

The new vancomycin guideline recommends monitoring for children based on data suggesting an association between increasing AUC₂₄ with kidney injury. There is not just one marker of kidney injury. Three of the most common ways to measure kidney function in pediatric patients include: Kidney Disease Improving Global Outcomes staging (KDIGO); Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) scores; and monitoring changes in serum creatinine and urine output.^{15,16} Serum creatinine is a delayed marker of changing glomerular filtration rate with a typical lag time of one to two days.¹⁷ Because it does not identify kidney injury until late in the process, serum creatinine is an imprecise measurement in

Table 1. 2020 Vancomycin Dosing for Serious Infections Caused by Methicillin-Resistant *Staphylococcus aureus* in Adult and Pediatric Patients³

	Adults	Pediatrics
Empiric dosing	15-20 mg/kg Q 8-12 hours = 30-40 mg/kg/day to 45-60 mg/kg/day*	3 months to < 12 years: 60-80 mg/kg/day Q 6 hours* ≥12 years to 18 years: 60-70 mg/kg/day Q 6-8 hours*
Loading dose	25-35 mg/kg in critically ill patients **	Consider 20 mg/kg for obese**
AUC goal	400-600 mg·h/L	400 mg·h/L
Empiric Maximum Daily Dose	4000-4500 mg/day	3000-3600 mg/day***

*Assumes patients have normal renal function, vancomycin is administered by intermittent infusion, and infection is responsive to a minimum inhibitory concentration less than 1 mg/L

**Prescribers can consider a 20 mg/kg loading dose (if significantly greater than initial dosing) before starting the maintenance dose, and they should investigate timing if it provides clinical value.³

***Most children will not need more than 3000 mg/day

patients with changing renal function who are developing kidney injuries. A patient's sex, weight, muscle mass, and age also affect serum creatinine, making the interpretation of a patient's result more complex. By creating their own definitions using validated tools (e.g., KDIGO, pRIFLE), hospitals can use a more individualized approach to determine if a patient has a kidney injury more accurately. Common themes among children who have experienced kidney injury are¹⁸

- vancomycin trough levels greater than 15 mg/L
- admission to the intensive care unit
- duration of vancomycin use longer than three to five days
- concurrent nephrotoxic medication (e.g., acyclovir, amikacin, amphotericin B, furosemide)

Cumulative Vancomycin Dose

Researchers have reported several risk factors that increase a pediatric patient's chance of developing nephrotoxicity, including higher cumulative vancomycin dose.^{19,20} In one study, researchers predicted kidney injury risk was 10% to 15% on day 5 of vancomycin treatment in all pediatric age groups (birth to age 18).¹⁹ These data sets reinforce the importance that patients should receive vancomycin treatment for the shortest duration needed to treat their infection. Providers should also de-escalate those without established need for vancomycin as soon as it is reasonable to prevent nephrotoxicity.

Critically Ill Patients

Another risk factor that increases vancomycin-related kidney injury risk in children is critical illness. Some data suggests that kidney injury in critically ill pediatric patients who receive vancomycin may be as high as 40%.¹³ (It is important not to interpret these data in a vacuum, as critically ill patients often have multiple risk factors for kidney injury.) Critically ill children often require longer therapy durations, have longer hospital stays, contract more severe infections, and are administered vasoactive medications (e.g., phenylephrine, norepinephrine, epinephrine, and dopamine) or other nephrotoxins (e.g., aminoglycosides, amphotericin B, piperacillin/tazobactam, furosemide). All of these can increase kidney injury risk. Pharmacy teams should make special note of concomitant vasoactive medications because they are commonly used in critically ill patients.¹³ **Table 3 (page 4)** reviews these medications and their relative risk associated with kidney injury in pediatric patients. Factors associated with a child's chances of developing kidney injury as defined by pRIFLE criteria while on vancomycin therapy include²¹

- shock at time of admission to pediatric intensive care unit
- presence of comorbidities
- vancomycin dose and serum levels
- use of concurrent nephrotoxins

The study that identified these factors also used a multivariate model that showed worsening renal function associated with vancomycin administration was reversible. The study also em-

SIDEBAR: Tech Talk

Area under the curve (AUC): Represents the patient's total drug exposure over a defined time interval (usually 24 hours), and it is a useful tool for therapeutic monitoring of drugs that may cause adverse events if blood levels exceed a certain exposure.

- Area under the curve in 24 hours (AUC₂₄): The patient's total drug exposure in 24 hours
- AUC₂₄/MIC = The ratio of AUC to MIC in a 24-hour time period. Clinicians use this term to calculate AUC more precisely. If local data determine that the MIC is more than or less than 1 mg/L, then providers can use the AUC₂₄/MIC as the target value for vancomycin dosing (AUC₂₄/MIC goal of 400) for greater accuracy.

Empiric dosing: The prescriber begins therapy (drug choice and dose) based on the educated guess for most likely diagnosis and organisms because culture or laboratory data is not yet available.

Loading dose (LD): A first dose higher than the calculated maintenance dose to boost the drug level in a patient's blood and tissues more quickly. All subsequent doses are at the calculated maintenance dose.

Methicillin-resistant *Staphylococcus aureus* (MRSA): A strain of the gram-positive *Staphylococcus aureus* bacteria that is resistant to the antibiotic methicillin (no longer used in humans) and most other commonly used antibiotics of the penicillin and cephalosporin classes.

Minimum inhibitory concentration (MIC): The lowest antibiotic concentration in blood needed to prevent visible bacterial growth. For most vancomycin-susceptible MRSA infections, the MIC is 1 mg/L or less. However, certain susceptible strains have MICs of 2 mg/L.

Steady state: When the amount of drug in the body stays within the same range (the amount in – the amount excreted) with continued dosing. For most antibiotics, like vancomycin, this occurs within a day or two of dosing.

Surrogate marker: An indirect indicator of a disease state or of its response to therapy when a more specific test either does not exist, is impractical, or is not cost effective.

Trough and peak level: The two extremes of blood stream levels. The trough level is the lowest drug concentration, measured immediately before the next scheduled dose. The peak level (measured or theoretical) is the highest concentration the patient will experience while on that dosing regimen.

Volume of distribution (Vd): The constant that relates the total amount of drug in the body to the plasma concentration of the drug at a given time. It reflects an individual drug's tendency to remain in the plasma or redistribute to other tissues.

phasized the multifactorial nature of kidney injury in critically ill patients because these patients may have numerous risk factors and sometimes receive multiple nephrotoxic medications. The multivariate model also reported that concomitant furosemide and/or amphotericin B administration was closely associated

Table 2. Recent Literature Comparing Empiric Dosing, AUC, and Trough Serum Concentrations in Pediatric Patients⁶⁻¹²

Pediatric Patient Population	Trough Level and AUC Value	Citation
Infants, median age 4.8 months, N = 70	Target attainment of > 400 mg·h/L was obtained in <ul style="list-style-type: none"> • 10% for troughs 5-10 mg/L • 71% for troughs 10-15 mg/L • 100% for troughs > 15 mg/L 	Alsultan A et al. 2019
Obese patients (≥ 70 kg), age 9.3 to 18.9 years with median weight 91.8 kg, N = 196	20.9 mg/kg (fat free mass) q6h or 13.3 mg/kg (total body weight) resulted in highly variable mean AUC range 159-685 mg·h/L and trough mean range 2-15.9 mg/L > 75% AUC met goal > 400 mg·h/L for 20 mg/kg q 6h, 25 mg/kg q 8h, 30 mg/kg q 8 h, 1000 mg q 6h, 1500 mg q 8h, 1500 mg q 6h based upon fat free mass	Moffett BS et al. 2019
Age 0.7-6.1 years old, N = 201	15 mg/kg q6h correlated to trough 9-12.9 mg/L and AUC ₂₄ /MIC ≥ 400 in > 90% of the pediatric patients when MIC was ≤ 1 mg/L	Zhang T et al. 2019
Patients aged 0.92-12.25 years old, N = 36	20 mg/kg/dose with a median interval of 6 hours resulted in median trough 11.4 mg/L and a median AUC/MIC 447 15 mg/kg/dose with a median interval of 6 hours had median trough 9.2 mg/L and AUC/MIC of 290 (MIC range 0.5-2 mg/L)	Kishk OA et al. 2017
Patients aged 3 months to <18 years old, N = 138	Initial median dose of 44 mg/kg/day every 6, 8 or 12 hours (n =17, 100, 14, respectively). Simulated Bayesian modeling produced an AUC median of 356 mg·h/L using the two-sample method and the median trough sample was 3.3 mg/L	Le J et al. 2014
Aged < 18 years old, 3 pharmacokinetic models simulating patients, N=5000	All 3 models estimated > 90% achieve AUC > 400 mg·h/L with a MIC of 1 mg/L with a dose of 15 mg/kg q6h, correlates to a trough of 7-10 microg/L	Frymoyer A et al. 2013
Ages 2.2-13.4 years, N=702	Empiric dosing of 60-70 mg/kg/day achieves AUC/MIC ≥ 400 in 75% of patients	Le J et al. 2013

with decreasing renal function.²¹

Pause and Ponder: When do you use vancomycin in your hospital? Do you think it is appropriate?

VANCOMYCIN DOSING CONSIDERATIONS

Past data suggested that overall vancomycin exposures (determined by trough monitoring) may have been higher than needed for adults, but common pediatric empiric dosing may have been too low. The revised vancomycin guideline suggests pediatric doses of 60 to 80 mg/kg/day divided every six hours for patients aged three to 12 months. It also recommends 60 to 70 mg/kg/day divided every six to eight hours for patients 12 to 18 years old (maximum 3 to 3.6 grams/day).³ Models have predicted these doses are more likely to achieve AUCs of 400 mg·h/L. Empiric dosing is complicated because providers must consider patient factors (e.g., age, weight, kidney function) to determine the appropriate maintenance dosing regimen (refer to [Table 2](#) for empiric dosing). Studies published in 2013 and 2014 demonstrated that patients younger than 12 years needed higher empiric doses of 60 to 80 mg/kg/day to consistently achieve AUC₂₄/MIC greater than 400.^{12,24} Children younger than 12 years old have higher clearance rates and thus eliminate the drug at a faster rate than older children. For those with renal dysfunction

Table 3. Drugs Associated with Increased Vancomycin Nephrotoxicity Risk^{13,19,21,22}

Nephrotoxic Drug	Incidence of AKI in patients with Concurrent Vancomycin Administration
Piperacillin/ tazobactam	65%
Contrast dye	61%
Amphotericin B	19%
Vasopressors	55%
Furosemide	71%
Acyclovir	0.29
Aminoglycosides	73%
NSAIDs	20%
Cyclosporine	27%

AKI=acute kidney injury, NSAIDs = non-steroidal anti-inflammatory drugs

(defined by serum creatinine at or below 0.9 mg/dL), researchers determined empiric initial dosages of 45 mg/kg/day may be sufficient.²⁴ Other researchers analyzed 56 mg/kg/day and 80 mg/kg/day doses, which resulted in 54.5% and 90.9% of children, respectively, reaching their goal target of AUC/MIC above 400 for MIC values ranging from 0.5 to 2 mg/L.⁹

These studies suggest empiric dosing and regimens with a goal AUC above 400 mg·h/L are a good starting point to provide sufficient vancomycin exposure for these patients.

Loading Dose

The new guideline continues to recommend loading doses for adult patients—specifically those who are critically ill—at a slightly different range than the 2009 guideline. Currently, the recommended loading dose is 20 to 35 mg/kg/dose for non-obese adults and 20 to 25 mg/kg/dose for obese adults (maximum of 3 grams) because obese patients have lower volumes of distribution than non-obese patients.^{3,4} Limited data exist in non-obese pediatric patients with regard to the use of loading doses. A research group investigated the concept of using a loading dose of 30 mg/kg in a small group of pediatric patients to achieve a target AUC₂₄/MIC of greater than 400. This double-blind randomized controlled trial compared a loading dose arm (n = 19) to traditional vancomycin dosing with an initial dose of 20 mg/kg (n = 27) in children 2 to 18 years old. Both groups received a maintenance regimen of 20 mg/kg/dose every eight hours, and both achieved a median level above the target AUC₂₄/MIC > 400. Two of the 19 pediatric patients in the loading dose group achieved a 15 to 20 mg/L trough prior to the second dose compared with none of the patients in the traditional dosing regimen (p = 0.17).²⁵ This small study provided preliminary information to suggest that loading doses may not help pediatric patients achieve target vancomycin exposure levels faster. Guidelines do not currently recommend loading doses in pediatric patients. The 2020 guideline advises that further studies are necessary to investigate the utility of loading doses and their timing prior to the maintenance dose at achieving target exposure faster and providing therapeutic benefit.³

For obese pediatric patients, the guideline suggests providers consider a loading dose of 20 mg/kg.³ This may confuse prescribers, given that recommended pediatric dosing every 6 to 8 hours works out to close to or exactly 20 mg/kg/dose anyways. The guideline indicates obese pediatric patients will have higher vancomycin exposures than non-obese pediatric patients, but more research is needed to determine if different empiric dosing regimens should be recommended.³

Obese Patients

Obese patients may need dose adjustments and closer monitoring because of lower volume of distribution. However, insufficient data indicates whether clinicians should use body surface area or body weight to calculate vancomycin dosing. In 2019, researchers analyzed data from obese pediatric patients who weighed more than 70 kg (median age 15.9 years old).⁷ They de-

SIDEBAR: Serum Trough Levels³

Prior to the 2020 update, serum trough levels served as surrogate markers for vancomycin's AUC levels. Providers measure serum trough levels just prior to the fourth dose (steady state conditions).

Since 2009, multiple studies have shown that vancomycin AUC₂₄ and trough levels correlate poorly in both adult and pediatric patients. Today, clinicians use a Bayesian calculator (based on probability) to calculate AUC₂₄ but some facilities and practitioners do not have access to such a tool.

Pause and Ponder: How can I monitor the AUC₂₄ exposure in my patients to ensure the target goal of AUC₂₄ 400 is met?

termined that the AUC₂₄ was highly variable. The data supported calculating fat free mass dosing, which incorporates patient age, BMI, and weight. The mean dose of 13.3 mg/kg/dose based on total body weight correlated to a mean dose of 20.9 mg/kg/dose using fat free mass. They also suggested that individualized dosing would be optimal for this patient population.⁷ The 2020 guideline advised a 20 mg/kg loading dose for obese pediatric patients to obtain optimal exposure in an appropriate time frame.³ If an obese pediatric patient requires a maintenance dose of less than 20 mg/kg, a 20 mg/kg loading dose may achieve the effective concentration faster. If the usual dose is more than 20 mg/kg, clinicians should use the higher (regular) dose instead.

Monitoring Adjustments

Prior to recent guideline updates, clinicians made adult and pediatric dosing adjustments when indicated based exclusively on trough concentrations.³ The guideline recommended 10 to 15 mg/L steady-state serum trough goals for adults for common infections. This goal increased to 15 to 20 mg/L for complicated infections (e.g., bacteremia, endocarditis, meningitis, osteomyelitis, and *S. aureus*-caused hospital acquired pneumonia). Many pediatric institutions implemented the same target trough goals for their patients.

This adult trough goal was originally designed to achieve an AUC₂₄/MIC of at least 400 for MIC of 1 mg/L or less.⁴ In 2017, researchers investigated trough concentrations in pediatric patients to establish a correlation between trough concentrations and mortality in confirmed MRSA cases. The results demonstrated that vancomycin serum trough concentrations below 10 mg/L were not associated with increased 30-day mortality for pediatric patients. They were, however, associated with prolonged duration of bacteremia compared with patients who had trough concentrations above 10 mg/L.²⁶ Another study analyzing vancomycin use in pediatric intensive care units in Switzerland determined that trough levels lower than 10 mg/L were, in fact,



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associated with increased mortality risk. The percentages of patients who died were 55.7%, 32.8%, and 11.5% with trough levels less than 10 mg/L, 10 to 20 mg/L and greater than 20 mg/L, respectively ($p = 0.0001$).²⁰ No studies indicate whether an AUC₂₄ target of less than 400 mg·h/L would fail to eradicate a MRSA infection. However, evidence of bacteremia in patients with lower trough concentrations (likely suggesting lower AUC) may support the 2020 recommendation to maintain exposure above 400 mg·h/L to prevent vancomycin resistance with subtherapeutic regimens.³

The 2020 guideline suggests that providers start therapeutic drug monitoring for pediatric patients with serious MRSA infections within 24 to 48 hours.³ The 2020 guideline recommends AUC-guided monitoring for pediatric patients with goal AUC levels between 400 and 600 mg·h/L. For institutions that have not yet adapted AUC monitoring, trough levels of less than 15 mg/dL are recommended. Prescribers must monitor patients closely to prevent subtherapeutic exposure, especially those with augmented renal clearance.³ Augmented renal clearance is a phenomenon observed in some critically ill patients whose kidneys clear certain medications more quickly than expected. In many cases, the patient's creatinine clearance is higher than expected based on their age, gender, and other factors. Clinicians observe augmented renal clearance most frequently in patients with neurologic damage, sepsis, major trauma, or burns. It may be associated with increased fluid administration, certain medications, and critical illnesses and may result in treatment failure pursuant to decreased drug concentrations, increased clearance, or shorter half-life. If augmented renal clearance occurs, patients will require dose adjustments.

To summarize and reiterate: The 2020 guideline has moved away from recommending trough alone as a surrogate marker for adult AUC₂₄. Instead, it suggests estimating AUC₂₄ for both

adult and pediatric patients. It suggests using one to two serum levels to adjust the vancomycin dosing based upon AUC calculations. Calculations incorporating two serum levels (one post distribution peak and a trough) to estimate AUC₂₄ exposure improve accuracy and sensitivity over trough-only levels.¹² The recommended goal AUC₂₄ is 400 to 600 mg·h/L for adults and 400 mg·h/L (with permissive maximum of 600 mg·h/L) for pediatric patients.³ Based upon reviewed literature, the guideline suggests that most pediatric patients should achieve an AUC₂₄ of 400 mg·h/L with maximum dose 3 grams/day (absolute maximum 3.6 grams/day).³ Investigators have formulated an equation to predict AUC₂₄ levels in pediatric patients to help guide empirical dosing for those with normal renal function.¹² Providers can predict AUC₂₄ levels using the patient's weight, serum creatinine level, age, and dose.

Options for AUC-Guided Dosing: Pediatrics

Various healthcare facilities use different systems to implement AUC-guided dosing into pediatric vancomycin monitoring. For adult patients, many free calculators are available online for vancomycin AUC₂₄ estimation. The vast majority cannot be used for pediatric patients because they incorporate different clearance or other assumptions specific to adult patients. Although paid pediatric-specific vancomycin AUC₂₄ calculators exist, the only free one known to the authors is for neonates (<http://neovanco.insight-rx.com/neo-vanco/>). It is limited to patients less than 52 weeks post-menstrual age (the time elapsed between the first day of the last menstrual period and birth) who have no major congenital heart or kidney disease. The other option is for pharmacists to calculate the AUC₂₄ manually using two levels. The new guideline suggests using the newer AUC₂₄ calculation systems using Bayesian modeling as reported in multiple studies. This modeling design incorporates the individual patient's pharmacokinetic parameters (e.g., volume of distribution, clearance) to optimize the estimated probability of distribu-

Table 4. Pediatric Patients and Vancomycin Pharmacokinetics^{7,8,10,12,27-30}

Patient Age Category (Citation)	Mean Volume of Distribution (L/kg)	Mean Clearance (L/kg/h)
Pediatric patients < 18 years old, median age 2.5 years; IQR 0.7 – 6.1 years (<i>Zhang et al. 2019</i>)	1.02	0.09
Pediatric patients aged < 18 years, mean age 7 years old, range 0.01 – 18 years (<i>Lamarre et al. 2000</i>)	0.27	0.16
Pediatric patients 3 months to 21 years old, median age 6.1 years; IQR 2.2 – 12.2 years (<i>Le et al. 2014</i>)	0.644 using Final PK Model	Range: 0.10-0.18
Pediatric patients < 18 years old, median age 6.6 years; IQR 2.2 – 13.4 years (<i>Le et al. 2013</i>)	<i>post hoc</i> Bayesian estimate 0.636	<i>post hoc</i> Bayesian estimate 0.12
Neonates and newborns ≥3 months old (<i>Marsot et al. 2012</i>)	0.430-0.864	Range: 0.057-0.080
Neonates ≥ 28 days old (<i>de Hoog et al. 2004</i>)	One-compartment: 0.764 Two-compartment: 0.496	N/A
Obese (> 95 th percentile for age and gender) pediatric patients < 18 years old, mean age 6.8 years ± 4.31 years (<i>Moffett et al. 2011</i>)	Range: 0.19-0.55	N/A

IQR=interquartile range; PK=pharmacokinetics

tion based on prior patients from a similar population. **Table 4** provides estimated volume of distribution and clearance values for various patient populations. Multiple online calculators use Bayesian modeling, but many have not yet been updated to include pediatrics. Thus, having access to values estimated in clinical trials is helpful for clinicians who are calculating by hand.

In 2014, a team of researchers investigated Bayesian modeling use in pediatric patients using one serum sample near trough and two serum samples, one near trough and one near peak. They determined that the AUC determination's accuracy was statistically superior with two samples ($p = 0.032$ for accuracy, $p = 0.325$ using internal validation sampling). The authors also used another analytic method—the rich sample method—and determined that two samples were statistically significant in accuracy and precision ($p = 0.020$ and $p = 0.013$, respectively).¹⁰ This experiment served as preliminary data to support using two samples for Bayesian calculations for accurate AUC predictions. The authors of the 2020 guideline advise entering peak and trough concentrations into Bayesian calculator programs to increase the calculations' accuracy until researchers conduct more studies to determine if a single time point is sufficient.³ Bayesian calculators are available for institutions to purchase, but can be expensive and delay transition from trough monitoring to AUC-based monitoring.

A *post hoc* Bayesian analysis identified mean volume of distribution estimations of 0.636 L/kg and clearance estimations of 0.12 L/kg/h from 702 patients (aged 3 months to 21 years).¹² As seen in **Table 4**, volume of distribution values vary depending on the disease state and patient population. It is prudent to individualize the parameters used before performing Bayesian calculations for AUC₂₄. More studies are needed in the pediatric population



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to improve the accuracy of this modeling paradigm. The 2020 guideline advises first-order pharmacokinetic equations with two concentrations or application of Bayesian estimation. The recent update advises vancomycin drug monitoring within 24 to 48 hours of drug initiation when patients have more serious infections and require higher AUC targets. It also advises vancomycin serum monitoring every eight to 48 hours and target trough ranges of 10 to 20 mg/kg to correlate with an AUC above 400 mg·h/L (assuming MIC of 1 mg/L).³

2020 GUIDELINE LIMITATIONS

While the guideline provides vancomycin dosing for pediatric patients, it still has several limitations. The updated guideline only covers disease caused by severe MRSA infections. This limits application of the dosing and monitoring targets for other types of infections that vancomycin covers, such as coagulase negative *Staphylococcus* species infections, pneumococcal meningitis, or enterococcal infections. In addition, only a few small, retrospective studies have analyzed unique pediatric vancomycin AUC₂₄ exposures (e.g., patients with more severe infections who require higher doses and longer treatment durations). This creates

a gray area of “risk vs. benefit” requiring clinical judgment to weigh nephrotoxicity risk against effective dosing when a more aggressive vancomycin dose is needed to clear infection. Another limitation to applying AUC-guided dosing in pediatrics is the inability to use some calculators available to assist in vancomycin dosing. Free online calculators may not apply to pediatric patients because they are programmed to address adult weights or clearances for accurate results. ClinCalc has several restrictions and indicates the calculator does not provide dosing for pediatrics and other populations accurately. The inability to use these calculators creates further obstacles for providers treating pediatric patients.

CONCLUSION

Updated empiric dosing for vancomycin is 60 to 80 mg/kg/day every 6 hours for pediatric patients aged 3 months to 12 years old and 60 to 70 mg/kg/day every 6 to 8 hours for those aged 12 to 18 years old. AUC₂₄-guided vancomycin dosing is advised for pediatric patients with a goal of 400 mg·h/L.

Figure 1. Being a Team Player when Kids Need Vancomycin

Best

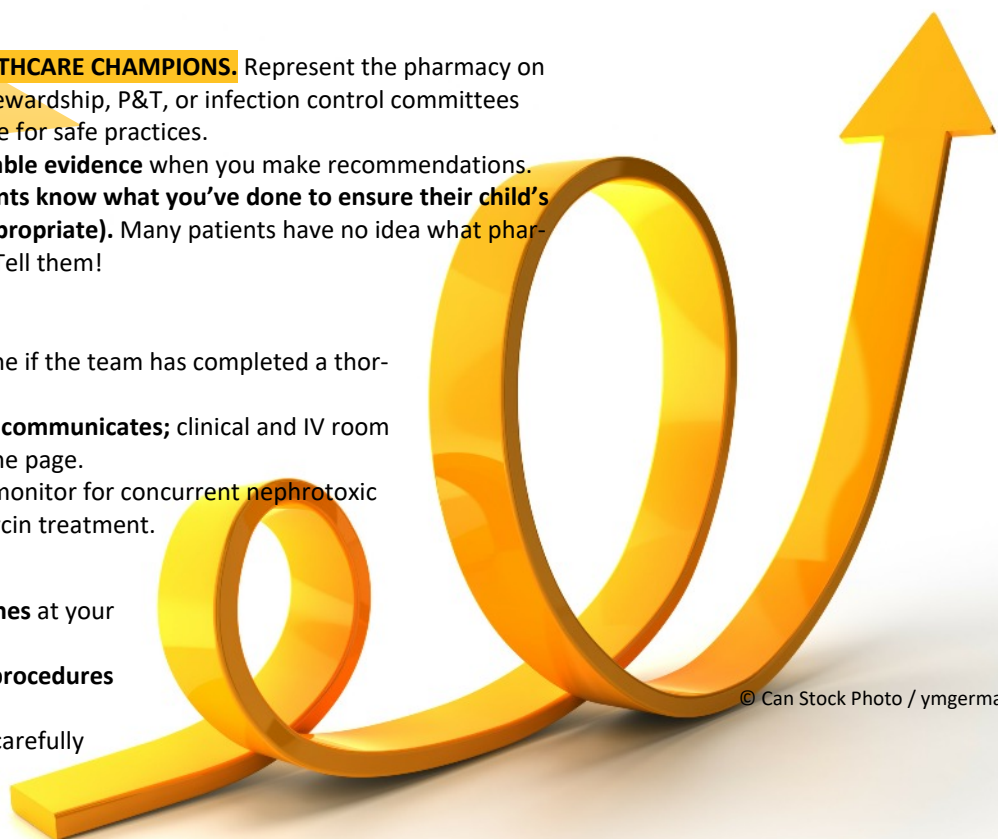
- 1 **BE HEALTHCARE CHAMPIONS.** Represent the pharmacy on antibiotic stewardship, P&T, or infection control committees and advocate for safe practices.
- 2 **Cite reliable evidence** when you make recommendations.
- 3 **Let parents know what you've done to ensure their child's safety (if appropriate).** Many patients have no idea what pharmacists do. Tell them!

Better

- 1 **Act quickly** to determine if the team has completed a thorough work up.
- 2 **Ensure pharmacy staff communicates;** clinical and IV room staff need to be on the same page.
- 3 **Use your database** to monitor for concurrent nephrotoxic drugs throughout vancomycin treatment.

Good

- 1 **Have updated vancomycin guidelines** at your fingertips.
- 2 **Know your hospital's policies and procedures** regarding vancomycin
- 3 **Double check** prescribers' orders carefully against the child's weight



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